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(54) Title: TOPICAL NASAL ANTIINFLAMMATORY COMPOSITIONS

(57) Abstract

The present invention provides topically applicable nasal compositions comprising a therapeutically effective amount of an antiinflammatory agent and a therapeutically effective amount of at least one agent selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anticholinergic agent, an anesthetic and a mucolytic agent. The present compositions are useful as nasal sprays and nose drops for the treatment of nasal and sinus conditions.

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TOPICAL NASAL ANTIINFLAMMATORY COMPOSITIONS

SPECIFICATION

BACKGROUND OF THE INVENTION

Topical nasal antiinflammatory preparations are known in the art for the treatment of inflammatory conditions of the nasal mucous membranes, and in particular for relief of the symptoms of nasal and sinus conditions such as rhinitis. However, nasal and sinus conditions may be characterized by diverse symptoms requiring treatment with multiple therapeutic agents. For example, allergic rhinitis may be characterized by rhinorrhea, nasal itching, sneezing, congestion and postnasal drip and treatment may require antihistamines, decongestants, antiallergics and anesthetics in addition to antiinflammatories.

The use of multiple topical nasal preparations to administer multiple therapeutic agents suffers from significant disadvantages. The volume of liquid that can effectively be applied nasally is limited by the surface area of the nostril and the bioadhesiveness of the liquid. In addition, a sufficient contact time between topical preparations and the surface area of the nostril is required to assure adequate dosing of a therapeutic agent. Further, spray formulations require a threshold surface tension to form droplets. Accordingly, the delivery volume per actuation is limited to the volume that will be retained in the nostril without premature drainage. Thus multiple topical nasal preparations cannot be effectively administered simultaneously.

Another disadvantage of the administration of multiple topical nasal preparations is patient inconvenience. Patient compliance may be compromised by the inconvenience of applying multiple spray products or nose drops. Patients complain when excess spray drains into their throats where it can be tasted, resulting in a need for flavor masking of bitter medicaments.

Accordingly, a need exists for a convenient means of nasal administration of multiple therapeutic agents.

SUMMARY OF THE INVENTION

The present invention provides topically applicable nasal compositions comprising a therapeutically effective amount of a topical antiinflammatory agent and a therapeutically effective amount of at least one agent suitable for topical nasal administration and selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, an anticholinergic agent, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anesthetic, and a mucolytic agent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides topically applicable nasal compositions comprising a topical antiinflammatory agent and at least one additional therapeutic agent. The present compositions are useful for the treatment of nasal and sinus conditions, for example allergic rhinitis or the common cold.

The topical antiinflammatory agents in the compositions of the present invention are corticosteroids known in the art to suppress inflammation. In a preferred embodiment the topical antiinflammatory agent is beclomethasone diproprionate, budesonide, dexamethasone, mometasone furoate, fluticasone proprionate or triamcinolone acetonide. The compositions contain a therapeutically effective amount of the selected antiinflammatory agent. Those of ordinary skill in the art can determine an amount that is therapeutically effective for the suppression of inflammation. The precise amount will depend upon the method of administration and the age, weight and condition of the subject to be treated. Generally the

antiinflammatory agents are utilized in dosages known in the art to be therapeutically effective upon nasal administration.

The compositions of the invention further comprise at least one additional therapeutic agent, and thus allow the convenient administration of an antiinflammatory agent and at least one additional therapeutic agent in a single topical nasal composition. The additional therapeutical agent is suitable for topical nasal administration and is selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, a leukotriene inhibitor, an anticholinergic agent, an antihistamine, an antiallergic agent, a local anesthetic and a mucolytic agent. The use of an additional therapeutic agent in combination with an antiinflammatory agent provides additive and synergistic effects in the treatment of nasal and sinus conditions.

Vasoconstrictors suitable for topical nasal administration in the compositions of the present invention are oxymetazoline naphazoline, xylometazoline, and phenylephrine. Leukotriene inhibitors include zafirlukast, a selective, competitive receptor antagonist of the three leukotrienes C4, D4, and E4; pranlukast, a selective, competitive receptor antagonist of D4; and zileuton, a leukotriene inhibitor. A. neuramidinase inhibitor includes zanamivir (GG-167). Suitable antihistamines are diphenhydramine, chlorpheniramine, cetirizine terfenadine, fenofexadine, astemizole norastemizole, azelastine, and azatidine. Antiallergic agents include cromolyn sodium and nedocromil levocabastine. An anticholinergic agent useful in the compositions of the present invention is ipratropium bromide. Local topical anesthetics include dyclonine, pramoxine, and benzocaine. Mucolytic agents suitable for topical nasal administration are acetylcysteine, guaifenisin and mucocysteine. The therapeutically effect amount of foregoing agents can be determined by the ordinarily skilled artisan with regard to the known use of these agents in the art and taking into account the method of administration and the age, weight and condition of the subject to be treated.

The compositions of the present invention are formulated as aqueous solutions comprising an antiinflammatory agent and at least one additional therapeutic agent and further comprising a pharmaceutically acceptable nasal carrier.

The formulation of pharmaceutical compositions is generally known in the art and reference can be conveniently made to standard text such as Remington's Pharmaceutical Sciences, 1985, 17th ed., Mack Publishing Co., Easton, Pennsylvania.

Preferred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier. The compositions are preferably isotonic. Isotonic agents such as a sugars and sodium chloride are known in the art and may be included in the subject compositions.

The compositions of the present invention may also contain a humectant to increase viscosity and effect moisturization and ciliary vitality. Suitable humectants include glycerin, polyethylene glycol, propylene glycol and mixtures thereof.

Additional agents including pharmaceutically acceptable preservatives, stabilizers, flavoring agents, and pH adjusters are known in the art and may be included in the present compositions.

Another embodiment of the present invention provides preservative-free compositions comprising an anti-inflammatory agent and at least one additional therapeutic agent. Preservative-free compositions are preferred due to reduced sensitivity and increased patient acceptance. These can be prepared in unit dose or in systems which prevent contamination of the reservoir of solution.

The compositions of the present invention can be conveniently administered nasally to a human subject in dosage unit form to elicit the desired therapeutic effect of the antiinflammatory agent and the additional therapeutic agents described above. The compositions may be administered in the form of a nasal spray or nose drops. Nasal sprays may be provided as squeeze bottles or metered dose manual nasal spray pumps designed to deliver the desired dose in one or two sprays, for example. The composition may also be administered as aerosol spray formulations, for example as metered dose pressurized aerosols containing propellants such as halogenated hydrocarbons.

WHAT IS CLAIMED IS:

1. A topically applicable nasal composition comprising a therapeutically effective amount of a topical antiinflammatory agent and a therapeutically effective amount of at least one agent suitable for topical nasal administration and selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an cholinergic agent, an anesthetic and a mucolytic agent.

2. The composition of Claim 1 wherein said topical antiinflammatory agent is selected from the group consisting of beclomethasone diproprionate, budesonide, dexamethasone, mometasone furoate, fluticasone proprionate and triamcinolone acetonide.

3. The composition of Claim 1 wherein said vasoconstrictor is selected from the group consisting of oxymetazoline, naphazoline, xylometazoline, and phenylephrine.

4. The composition of Claim 1 wherein said antihistamine is selected from the group consisting of diphenhydramine, chlorpheniramine, terfenadine, azelastine, norastemizole, fexofenadine, cetirazine, astemizole and azatidine.

5. The composition of Claim 1 wherein said antiallergic agent is selected from the group consisting of cromolyn sodium, levocabastine, and nedocromil.

6. The composition of Claim 1 wherein said anticholinergic agent is ipratropium.

7. The composition of Claim 1 wherein said topical anesthetic is selected from the group consisting of dyclonine, pramosine, and benzocaine.

8. The composition of Claim 1 wherein said mucolytic agent is selected from the group consisting of acetylcysteine, guaifenesin and mucocysteine.

9. The composition of Claim 1 wherein said leukotriene inhibitor is selected from the group consisting of zafirlukast, pranlukah, and zileuton.

10. The composition of Claim 1 wherein said neuramidinace inhibitor is zanamivir.

11. A topically applicable nasal composition comprising a therapeutically effective amount of a topical antiinflammatory agent selected from the group consisting of beclomethasone diproprionate, budesonide, dexamethasone, mometasone furoate, fluticasone proprionate and triamcinolone acetonide and a therapeutically effective amount of at least one agent selected from the group consisting of oxymetazoline, phenylephrine, diphenhydramine, chlorpheniramine, terfenadine, astemizole, azatidine, cromolyn sodium, nedocromil, ipratropium bromide, dyclonine, benzocaine, acetylcysteine, guaifenesin and mucocysteine.

12. The composition of Claim 1 or 11 further comprising at least one humectant.

13. The composition of Claim 12 wherein said humectant is selected from the group consisting of glycerin, polyethylene glycol and propylene glycol.

14. The composition of Claim 1 or 11 comprising a pharmaceutically acceptable carrier.

15. The composition of Claim 1 or 11 formulated for application as a nasal spray.

16. The composition of Claim 1 or 11 formulated for application as nose drops.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06 A61K31/57 A61K31/58 A61K31/135 A61K31/35
A61K31/245 A61K31/09 A61K31/38 A61K31/195 A61K31/47
A61K31/445 A61K31/55 A61K31/44 A61K31/615 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 01337 A (MCNEIL-PPC, INC.) 16 January 1997 see abstract see page 2, line 8 - line 18 see page 8, line 2 - line 24	1,2,4, 11-16
X	WO 97 01341 A (MCNEIL-PPC, INC.) 16 January 1997 see page 2, line 5 - line 14 see page 8, line 2 - line 19	1,2,5, 11-16
X	WO 93 09764 A (CENTER FOR INNOVATIVE TECHNOLOGY) 27 May 1993 see page 6, line 10 - line 14 see page 6, line 30 see page 22, line 23 - line 33 see page 26, line 23 - line 25 see claims 1,2,4-8,13-23	1,3,4,6, 14-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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